NATIONAL CANCER INSTITUTE

NCI Cancer Bulletin

Eliminating the Suffering and Death Due to Cancer

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Obesity Associated with Higher Cancer Risk among Veterans

In a study of 4.5 million patients hospitalized at Veterans Affairs hospitals over a 27-year time period, researchers found an increased risk for nearly 20 different cancers in those men who were obese. The study appears in the January/February issue of *Cancer Causes and Control*. Claudine Samanic and co-workers, all from the National Cancer Institute's (NCI's) Division of Cancer Epidemiology and Genetics, examined medical histories from computerized discharge notes from Veterans Affairs hospitals across the country. They assessed records for over 3.6 million white men and over 800,000 black men. Among obese veterans, they found an increased risk for cancers of the colon and kidney, which have been reported in numerous other studies, but also an increased risk for a number of less common cancers, such as male

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Director's Update

Energy Balance: The Complex Interaction of Diet, Physical Activity, and Genetics in Cancer Prevention and Control

At a time when nearly two-thirds of the U.S. population is considered overweight or obese, compelling evidence suggests that excess body weight is a risk factor for many cancers. However, in terms of weight-related factors, body weight alone does not completely determine an individual's ability to prevent or survive cancer. Instead, cancer researchers use the term "energy balance" to describe the complex interaction among diet, physical activity,

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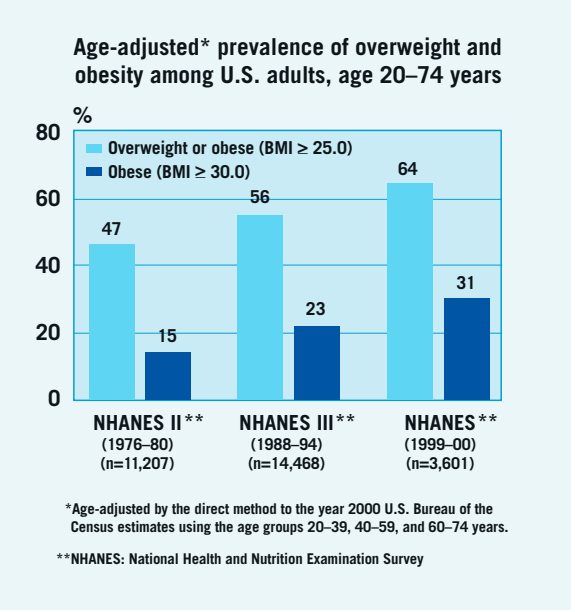

Source: Centers for Disease Control and Prevention

(*Obesity Associated with Cancer Risk among Veterans continued from page 1)*
breast, lower esophagus, gallbladder, thyroid, extrahepatic bile duct, and connective tissue cancers, as well as malignant melanoma, multiple myeloma, chronic lymphocytic leukemia, and acute myeloid leukemia.

For most tumors, the obesity-related patterns of risk were similar among black and white men. The researchers noted that the mechanisms by which obesity predisposes men to cancer are likely to vary by the type of cancer. They postulated that metabolic alterations associated with obesity and excess abdominal fat may be related to the increased risk for some cancers, possibly through the development of insulin resistance and other mechanisms.

The researchers expressed a number of cautions in interpreting the study results, including the lack of a system to follow the men once they have been discharged from the Veterans Affairs hospitals, which may result in incomplete cancer profiles. Further investigation is needed to clarify the impact of excess body weight, particularly on the risk of relatively uncommon forms of cancer, and to determine the mechanisms involved. ◆

January 18–24 is
Healthy Weight Week

For more information, please visit:

http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt

(*Director's Update continued from page 1)*
and genetics on growth and body weight over an individual's lifetime and how those factors may influence cancer risk.

NCI has supported epidemiologic research in large cohort and case-control studies looking at the effects of weight, diet, physical activity, and cancer outcomes. These and other studies suggest that being overweight or obese increases the risk for postmenopausal breast cancer, colon cancer, adenocarcinoma of the esophagus, endometrial cancer, renal cell carcinoma, and several other cancers. Other studies, including some basic animal and cell culture studies, have explored the mechanisms by which obesity may influence cancer risk. Clinical intervention studies involving small groups of patients have placed people on specific diet, activity, and weight-control regimens to see how those factors influence cancer risk. This research is promising and should yield great insights into how these particular behavioral and genetic factors contribute to the cancer burden.

As is often the case, this research has raised as many questions as it has answered. It is abundantly clear, however, that regular physical activity can reduce the risk of colon cancer by half, and can also reduce the risk of breast cancer among obese postmenopausal women. Additionally, we know that balancing "energy in/energy out"—the calories eaten vs. those burned each day—is imperative to avoid gaining weight. For many Americans who are overweight and sedentary, eating fewer calories and increasing physical activity is necessary to reach a healthy weight.

The nation's obesity epidemic has heightened our interest in obesity and energy balance at both NIH and NCI. In 2002, NCI formed a group to identify priorities for obesity and cancer research. The group identified three goals: to understand the causes of adverse patterns of weight, physical activity, and diet; define how these causes contribute to cancer; and apply this knowledge to prevent and control cancer. We hope to understand how obesity can interact over the entire lifetime to influence the cancer process, and to develop better measures of weight, diet, and physical activity. To do this, NCI will continue to work actively with NIH and other federal and private partners to complement and extend existing efforts.

In 2005, NCI anticipates receiving funding for transdisciplinary centers on energetics and cancer. The centers will bring together scientists from multiple disciplines to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet. The centers also will provide significant opportunities to train scientists at every stage in their careers in the area of energy balance and cancer. NCI is also now developing an energy balance intervention dissemination initiative to actively disseminate evidence-based interventions for obesity.

I invite you to learn more about NCI's energy balance initiative, including research plans and progress, in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2005* at: http://cancer.gov/pdf/nci_2005_plan. ◆

Andrew C. von Eschenbach, M.D.
Director, National Cancer Institute

Cancer Research Highlights

Human Cells Producing Proteins

In the January 15 issue of *Nature*, NCI scientists reported the discovery of a new mechanism in human cells for producing proteins. This involves cutting a protein into smaller pieces, which are then rejoined in a different order. The finding suggests that human cells may be able to produce a far greater range of proteins than was previously thought. Two of the authors, Dr. Ken-ichi Hanada and Dr. James C. Yang, are from NCI's Surgery Branch.

The researchers were studying fragments of a protein known as fibroblast growth factor-5 (FGF-5), which was overproduced in the tumor cells of a kidney cancer patient. In the process of trying to determine which portion of the FGF-5 protein is recognized by the patient's killer T cells, they discovered that the T cells recognize two stretches of the protein that are not next to each other. This led them to conclude that after the FGF-5 protein is produced in the cell, it is cut into pieces, which are then stitched together in a different order. The enzymes for cleaving the protein or stitching the pieces back together are not known. Similar protein processing has been reported in single-celled organisms and some plants.

Novel Mechanism Allows HTLV-1 to Mask Its Presence

The human T-cell leukemia/lymphoma virus type 1 (HTLV-1) has evolved to develop a novel mechanism for inhibiting its expression, a function that may mask its presence in infected cells, researchers from the NCI report in the January 2004 issue of *Nature Medicine*. The finding may explain why HTLV-1 can persist despite the body's robust immune response to it.

Dr. Genoveffa Franchini and colleagues from the Animal Models and Retroviral Vaccines Section, Center for Cancer Research, found that a nuclear-resident protein of HTLV-1, p30II, is able to reduce the levels of the Tax and Rex proteins, which play critical roles in virus expression.

"This protein is able to modulate viral expression and may help the virus to remain concealed and avoid elimination by the host immune system," Dr. Franchini said. The researchers studied p30II's effect at the post-transcriptional level as well as during transcription. The finding was that the real action was occurring after transcription of viral messenger RNAs, with p30II specifically targeting the Tax and Rex mRNA, but strictly in the cell nucleus.

The novelty of this finding, Dr. Franchini explained, is that retroviruses are thought to become latent through cellular mechanisms, "leaving it to the cell to decide its own fate." The protein p30II "puts the virus more in charge of what it wants to do." A high viral replication correlates with a higher probability of developing leukemia. Therapies that can block the interaction of p30II with the viral RNA, Dr. Franchini suggested, will unmask the virus, "meaning the virus will be expressed and more overt to the immune system, and that might facilitate its elimination."

Smoking Reduction Fails to Proportionally Decrease Carcinogen Exposure

The good news from a study in the January 21 issue of the *Journal of the National Cancer Institute* (*JNCI*) is that exposure to the potent tobacco carcinogen NNK can be significantly reduced in smokers who substantially reduce their daily cigarette intake. The bad news, according to the University of Minnesota Cancer Center researchers who conducted the NCI-funded study, is that the reduction is not proportional to the reduction in cigarettes smoked. In a related *JNCI* commentary, an international team of epidemiologists reported that a review of the evidence accumulated over the past 16 years reveals that there is a causal relationship between tobacco use and cancers not previously believed to be associated with smoking, including myeloid leukemia and cancers of the stomach and liver.

"Together, these articles serve as a poignant reminder that tobacco's role as a cancer initiator and promoter… remains one of the greatest global public health challenges," wrote Drs. Scott Leischow and Mirjana Djordjevic, of the NCI Tobacco Control Research Branch, in an accompanying editorial. "The most dramatic health benefits in the next half century will occur if we can significantly increase the number of smokers who quit." ◆

Special Report

NCI Re-engineering Intramural Research Program

A strong basic science foundation coupled closely with innovative technology development, outstanding clinical investigators, and population scientists afford NCI's Intramural Research Program (IRP) a unique opportunity to help achieve NCI's challenge goal of eliminating the suffering and death due to cancer by 2015. Encompassing the Division of Cancer Epidemiology and Genetics (DCEG) and the Center for Cancer Research (CCR), the IRP is uniquely positioned to create a premier center of cancer research that can pioneer novel approaches to translational and clinical research through its interdisciplinary research strengths and that can provide outstanding training in basic, clinical, epidemiologic, and translational research.

To enhance the scientific environment so it nurtures innovative, high-risk, and long-term basic, clinical, and population-based research with an emphasis on translational initiatives that bridge all approaches, the IRP is engaging in a "re-engineering" process. This re-engineering process builds on the critical core of investigators dedicated solely to basic, clinical, and epidemiologic research, while enhancing and accelerating work for those engaged in interdisciplinary and multidisciplinary translational research.

According to Dr. J. Carl Barrett, director of CCR, re-engineering capitalizes on "the recognized areas of research excellence in the IRP and provides the foundation upon which NCI can establish a leadership role in multidisciplinary and interdisciplinary translational research." This theme is underscored by Dr. Joseph F. Fraumeni, Jr., director of DCEG, who indicated that "the IRP will take advantage of its concentration of cancer epidemiologists, biologists, and clinicians to form transdisciplinary research teams that can quickly and efficiently translate discoveries in basic science into medical and public health strategies aimed at cancer prevention, detection, and treatment."

Dr. J. Carl Barrett
Director, Center for Cancer Research

Although the traditional administrative organization of the IRP remains, cross-organizational faculties and working groups now provide a forum where scientists from diverse backgrounds can work cooperatively in a particular discipline, disease, or approach to scientific discovery. The re-engineering is creating "an IRP without walls, that fosters the exchange of ideas among intramural and extramural scientists and clinicians," according to Dr. Barrett.

"Re-engineering the IRP is an ongoing process designed to create effective interactions among its scientists as well as with investigators in the extramural divisions, in other NIH institutes, academic institutions, and industry," said Dr. Barrett. According to Dr. Fraumeni, "NCI is well positioned as a national agency to accelerate progress through strategic partnerships between intramural and extramural scientists that integrate population and clinical sciences with the tools of genomics and other emerging technologies."

Other initiatives also contribute to the enhanced collaboration encouraged by re-engineering. A total of four Centers of Excellence in advanced biomedical technology, molecular epidemiology, immunology, and molecular oncology have been established to support basic and translational research to reach the 2015 challenge goal. Additionally, the intramural clinical research program has been enhanced by establishment of the Medical Oncology Clinical Research Unit (MOCRU), a trans-organizational structure that provides investigators throughout NCI with centralized access to clinical research expertise and medical oncology resources. MOCRU acts as a clinical partner to intramural investigators, promoting

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(*Special Report continued from page 4)*
translation of laboratory discoveries into the clinical setting and establishing standards of excellence for clinical research and patient care. Intramural clinical studies continue to be based on innovative, concept-based clinical research trials applicable to the treatment of many cancer types and have an emphasis on rapid translation of basic research discoveries to clinical applications.

Cross-disciplinary training and enhanced communication are critical to the re-engineering process. The IRP provides traditional basic, clinical, and epidemiologic research training, but also training in interdisciplinary and translational research to help prepare the next generation of national leaders in cancer research. The IRP provides trainees with access to novel approaches and cutting-edge technologies (e.g., imaging, nanotechnology, and computational biology) and encourages trainees to have multiple mentors with expertise in diverse fields of study. NCI's educational objectives are achieved through numerous activities designed to increase interactions with the extramural community and assist scientists in achieving career goals. Activities include partnerships, courses and workshops, fellowship programs with special emphasis, and career development activities.

The re-engineered IRP will reward investigators for their scientific creativity, collaborative interdisciplinary and multidisciplinary research, willingness to take risks, and efforts to try novel research approaches. Programs that cut across labs, branches, and divisions are of immense value to the IRP and are important for scientific progress. ◆

Featured Clinical Trial

Name of the Trial
Phase III Randomized Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer (NSABP-P-2). See the protocol summary at http://cancer.gov/clinicaltrials/NSABP-P-2.

Principal Investigator
Dr. Norman Wolmark, chairman, National Surgical Adjuvant Breast and Bowel Project (NSABP)

Why Is This Trial Important?
In 1998, results from the Breast Cancer Prevention Trial showed that tamoxifen (brand name Nolvadex®) reduced the chance of developing breast cancer by about half in premenopausal and postmenopausal women at increased risk of breast cancer. Large studies testing the effectiveness of raloxifene (brand name Evista®) against osteoporosis have shown that the drug reduces the incidence of breast cancer in postmenopausal women with a history of osteoporosis.

NSABP

Norman Wolmark
STAR Principal Investigator

STAR will determine whether the osteoporosis prevention drug raloxifene is as effective as the cancer prevention drug tamoxifen in reducing the chance of developing breast cancer in postmenopausal women.

"Another important part of STAR will be to assess the long-term safety of raloxifene versus tamoxifen in women at increased risk of breast cancer," said Dr. Wolmark of NSABP, the group of researchers conducting the trial. "The two drugs have different side effects, which we need to better understand."

Who Can Join This Trial?
STAR will include 19,000 postmenopausal women age 35 and older who are at high risk for developing breast cancer. More than 17,500 have already joined the trial since it opened in 1999. See the full list of eligibility criteria for this trial at http://cancer.gov/clinicaltrials/NSABP-P-2.

Where Is This Trial Taking Place?
More than 500 sites in the United States, Puerto Rico, and Canada are enrolling participants in STAR. See the list of study sites at http://cancer.gov/clinicaltrials/NSABP-P-2.

Who to Contact
See the list of study contacts at http://cancer.gov/clinicaltrials/NSABP-P-2 or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The call is toll-free and completely confidential. Information is also available at NSABP's Web site about breast cancer prevention or NSABP's Web page about STAR. ◆

Funding Opportunities

The Early Detection Research Network (EDRN): Clinical Epidemiology and Validation Centers

RFA-CA-05-005
Application Receipt Date: June 14, 2004

NCI seeks U01/U24 applications for new and competing renewals of the Clinical Epidemiology and Validation Centers (CECs) component of EDRN. Supporting collaborative translational research, EDRN is responsible for the development, evaluation, and validation of biomarkers for earlier cancer detection and risk assessment. The CECs serve as resource centers for specimens for use in EDRN and either participate in or develop the validation studies.

For more information see http://cri.nci.nih.gov/index.cfm.
Inquiries: Dr. Sudhir Srivastava, srivasts@mail.nih.gov

Innovative Technologies for Molecular Analysis of Cancer (SBIR/STTR)

RFA-CA-05-006
Letter of Intent Receipt Dates: Feb. 10, 2004; May 17, 2004; Sept. 17, 2004
Application Receipt Dates: March 10, 2004; June 17, 2004; Oct. 18, 2004

NCI invites applications for projects to develop highly innovative cancer-relevant research technologies, methods, and tools that support molecular analysis in vitro, in situ, or in vivo in discovery processes, as well as in preclinical models and clinical research. The RFA will use the SBIR and STTR mechanisms. For more information see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=1800.
Inquiries: Dr. Gregory J. Downing, OTIR; downingg@mail.nih.gov

Application of Emerging Technologies for Cancer Research (SBIR/STTR)

RFA-CA-05-007
Letter of Intent Receipt Dates: Feb. 10, 2004; May 17, 2004; Sept. 17, 2004
Application Receipt Dates: March 10, 2004; June 17, 2004; Oct. 18, 2004

NCI invites applications for projects to evaluate the use of emerging technologies ready for initial application to clinical or biological questions in cancer research. Applicants should demonstrate that the technology is robust and yields reproducible measurements and should gather preliminary data to support use of the technology in a future project(s) with a clinical or biological focus. The RFA will use SBIR and STTR mechanisms. For more information see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=1801.
Inquiries: Dr. Gregory J. Downing, OTIR; downingg@mail.nih.gov

Innovations in Cancer Sample Preparation (SBIR/STTR)

RFA-CA-05-008
Letter of Intent Receipt Dates: Feb. 10, 2004; May 17, 2004; Sept. 17, 2004
Application Receipt Dates: March 10, 2004; June 17, 2004; Oct. 18, 2004

NCI invites applications for research projects to develop, enhance, or adapt sample preparation methodologies and technologies; develop assays to assess sample quality; and elucidate criteria by which to judge sample quality. The outcome will be products and methods to optimize sample utility. The RFA will use the SBIR and STTR mechanisms. For more information see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=1802.
Inquiries: Dr. Gregory J. Downing, OTIR; downingg@mail.nih.gov

NCI Competing Continuation SBIR/STTR Phase II Grants for Cancer Diagnosis, Prevention, and Treatment

PA-04-047
Letter of Intent Receipt Dates: March 1, 2004; July 1, 2004; Nov. 1, 2004; March 1, 2005; July 1, 2005; Nov. 1, 2005
Application Receipt Dates: April 1, 2004; Aug. 1, 2004; Dec. 1, 2004; April 1, 2005; Aug. 1, 2005; Dec. 1, 2005

The purpose of this Program Announcement (PA) is to solicit grant applications for the competing continuation of projects from previously funded phase II projects for the process of developing products for commercialization and translation into the clinic.

The PA will use the SBIR and STTR Phase II Grants award mechanism.

For more information see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=1780.
Inquiries: Rosemary Wong, rw26f@nih.gov ◆

NCI Notes

Proteomics Slated for Science Writers' Seminar

An update on clinical proteomics will be presented at the NCI Science Writers' Seminar on January 28, 2004.

These sessions are designed for science and medical reporters with the intent of increasing the quality and quantity of media coverage on cancer research. The speakers will be **Dr. Lance Liotta** and **Dr. Emanuel Petricoin**, codirectors of the NCI/Food and Drug Administration Clinical Proteomics Program, and their collaborator **Dr. Elise Kohn**, from the NCI Laboratory of Pathology.

The scientists will explain their successes in distinguishing ovarian, breast, and prostate cancers from benign conditions and how their techniques can be used to clinically identify early-stage cancers. They will highlight progress since their 2002 landmark paper in *The Lancet*, which first described proteomics for possible use in detecting ovarian cancer. The seminar will be held from 11 a.m. to 1:30 p.m. on the NIH campus in Bethesda at the Natcher Conference Center, Room F1. Pre-registration is required for on-site attendance, but anyone can watch the live webcast at http://videocast.nih.gov/.

President's Cancer Panel Focuses on Survivorship

Cancer survivors of all ages share many of the same concerns, the President's Cancer Panel concluded after its series of meetings on cancer survivorship in 2003 and into 2004. The latest meeting on this topic, held in Philadelphia in January 2004, focused on older adult survivors; earlier events examined concerns of adults, adolescents, and young survivors.

The panel has heard of the difficulties all survivors endure: transferring treatment records to their community providers, accessing relevant post-treatment information, obtaining appropriate follow-up screening and care, acquiring necessary support services, overcoming financial and insurance-related barriers, and addressing cultural and language barriers to care.

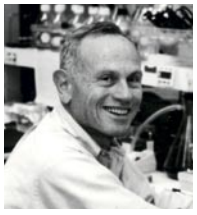
Specific issues affect survivors ages 60 and older. Survivors in this age group told the panel of the hardships of living on a fixed income. They also expressed their fears of losing their employment and associated insurance benefits. They called for improved communication with the public—employers, caregivers, and insurers—about the experiences and needs of cancer survivors.

Older adult survivors have more co-morbidity issues, which may obscure symptoms of recurrence. They metabolize pharmacologic agents differently than younger people. And they are more concerned about transmitting genetically linked cancers to their children.

The panel's final report on cancer survivorship is expected to be released this summer.

Sporn Named First NCI Eminent Scholar

Dr. Michael B. Sporn, of Dartmouth Medical School, has been appointed as the first NCI Eminent Scholar at the NCI Center for Cancer Research (CCR). As part of the re-engineering of the Intramural Research Program (IRP), the scholar program was established to allow close interactions and collaborations between distinguished extramural and NCI IRP scientists. The formal inclusion of extramural scientists within the IRP fosters the exchange of ideas among basic, translational, and clinical researchers. Scholars interact on a regular basis with the intramural scientists, faculties, and training programs. They may mentor fellows and play a direct role in IRP research programs.



Joseph Mehling

Awards

Nobel Laureate **Dr. Leland H. Hartwell**, Fred Hutchinson Cancer Research Center, received the Alfred Knudson Award in Cancer Genetics at the NCI Combined Intramural Principal Investigator Retreat on January 16. Dr. Hartwell addressed nearly 600 staff members of the NCI intramural program about the prospects of eliminating cancer. The award recognizes Dr. Hartwell for pioneering genetic and molecular studies uncovering the regulation of cell division. The award was created to foster the development of research programs in cancer genetics. It was named after Dr. Knudson, who revolutionized the understanding of the genetic basis of cancer, especially through his groundbreaking work which led to the discovery of tumor suppressor genes, and who served at NCI in the late 1990s.

Also at the retreat, **Dr. Janet D. Rowley**, University of Chicago, an expert on human chromosome analysis, accepted the Rosalind E. Franklin Award for Women in Cancer Research. Dr. Rowley, an Albert Lasker Award recipient, is internationally known for her discovery that the translocation of genetic material seen in the Philadelphia chromosome is the cause, not the result, of chronic myelogenous leukemia. The NCI prize honors the commitment of women in cancer research and is given in tribute to Dr. Franklin, who played a critical role in the discovery of the DNA double helix. ◆

Featured Meetings

This is a list of selected scientific meetings sponsored by NCI and other organizations. For locations and times and a more complete list of scientific meetings, including NCI's weekly seminars and presentations open to the public, see the NCI Calendar of Scientific Meetings at http://calendar.cancer.gov.

2004 NCI Advisory Committee Upcoming Meetings January–March

Date	Advisory Committee
Jan 22	Advisory Committee to the Director, NCI
Feb 17-19	National Cancer Advisory Board
Mar 15-16	Clinical Sciences and Epidemiology—Subcommittee 1, Board of Scientific Counselors, NCI
Mar 15-16	Basic Sciences—Subcommittee 2, Board of Scientific Counselors, NCI
Mar 15-16	NCI Board of Scientific Advisors

Selected Upcoming Meetings of Interest

Date	Meeting	Speaker(s)
Jan 28	Building the Interface of Nanotechnology and Cancer Imaging Research Symposium	Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives
Jan 29-30	Fifth National Forum on Biomedical Imaging in Oncology	Dr. Ellen Feigal, Acting Director, Division of Cancer Treatment and Diagnosis
Jan 30-Feb 1	American Psychosocial Oncology Society First Annual Conference: Advancing Multidisciplinary Approaches to Psychosocial Oncology	Dr. Andrew C. von Eschenbach, Director
Feb 2	Director's Seminar Series: Progress with a Purpose	Dr. Mark B. McClellan, Commissioner of Food and Drugs, U.S. Food and Drug Administration
Feb 4-7	Sixth International Conference on Pain and Chemical Dependency	Dr. Harold P. Freeman, Director, Center to Reduce Cancer Health Disparities

NCI Exhibits

NCI Exhibits are presented at various professional and society meetings. Further information about the NCI Exhibits Program can be found at: http://exhibits.cancer.gov.

This *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads a national effort to eliminate the suffering and death due to cancer. Through basic and clinical biomedical research and training, NCI conducts and supports research that will lead to a future in which we can prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://cancer.gov.

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